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(57) Abstract

The present invention is directed to compounds which inhibit farnesyl-protein transferase (FTase) and the farnesylation of the oncogene protein Ras. The invention is further directed to chemotherapeutic compositions containing the compounds of this invention and methods for inhibiting farnesyl-protein transferase and treatment of cancer.

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TITLE OF THE INVENTION

INHIBITORS OF FARNESYL-PROTEIN TRANSFERASE

BACKGROUND OF THE INVENTION

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The Ras gene is found activated in many human cancers, including colorectal carcinoma, exocrine pancreatic carcinoma, and myeloid leukemias. Biological and biochemical studies of Ras action indicate that Ras functions like a G-regulatory protein, since Ras must be localized in the plasma membrane and must bind with GTP in order to transform cells (Gibbs, J. et al., Microbiol. Rev. 53:171-286 (1989)). Forms of Ras in cancer cells have mutations that distinguish the protein from Ras in normal cells.

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At least 3 post-translational modifications are involved with Ras membrane localization, and all 3 modifications occur at the C-terminus of Ras. The Ras C-terminus contains a sequence motif termed a "CAAX" or "Cys-Aaa¹-Aaa²-Xaa" box (Aaa is an aliphatic amino acid, the Xaa is any amino acid) (Willumsen et al., Nature 310:583-586 (1984)). Other proteins having this motif include the Ras-related GTP-binding proteins such as Rho, fungal mating factors, the nuclear lamins, and the gamma subunit of transducin.

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Farnesylation of Ras by the isoprenoid farnesyl pyrophosphate (FPP) occurs *in vivo* on Cys to form a thioether linkage (Hancock et al., Cell 57:1167 (1989); Casey et al., Proc. Natl. Acad. Sci. USA 86:8323 (1989)). In addition, Ha-Ras and N-Ras are palmitoylated via formation of a thioester on a Cys residue near a C-terminal Cys farnesyl acceptor (Gutierrez et al., EMBO J. 8:1093-1098 (1989); Hancock et al., Cell 57:1167-1177 (1989)). Ki-Ras lacks the palmitate acceptor Cys. The last 3 amino acids at the Ras C-terminal end are removed proteolytically, and methyl esterification occurs at the new C-terminus (Hancock et al., *ibid*). Fungal mating factor and mammalian nuclear lamins undergo identical modification steps (Anderegg et al., J. Biol. Chem. 263:18236 (1988); Farnsworth et al., J. Biol. Chem. 264:20422 (1989)).

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Inhibition of Ras farnesylation in vivo has been demonstrated with lovastatin (Merck & Co., Rahway, NJ) and compactin (Hancock et al., ibid; Casey et al., ibid; Schafer et al., Science 245:379 (1989)). These drugs inhibit HMG-CoA reductase, the rate
5 limiting enzyme for the production of polyisoprenoids and the farnesyl
pyrophosphate precursor. It has been shown that a farnesyl-protein transferase using farnesyl pyrophosphate as a precursor is responsible for Ras farnesylation. (Reiss et al., Cell, 62: 81-88 (1990); Schaber et al., J. Biol. Chem., 265:14701-14704 (1990); Schafer et al., Science,
10 249: 1133-1139 (1990); Manne et al., Proc. Natl. Acad. Sci USA, 87:7541-7545 (1990)).

Inhibition of farnesyl-protein transferase and, thereby, of farnesylation of the Ras protein, blocks the ability of Ras to transform
15 normal cells to cancer cells. The compounds of the invention inhibit Ras farnesylation and, thereby, generate soluble Ras which, as indicated infra, can act as a dominant negative inhibitor of Ras function. While soluble Ras in cancer cells can become a dominant negative inhibitor, soluble Ras in normal cells would not be an inhibitor.

A cytosol-localized (no Cys-Aaa¹-Aaa²-Xaa box membrane domain present) and activated (impaired GTPase activity, staying bound to GTP) form of Ras acts as a dominant negative Ras inhibitor of
20 membrane-bound Ras function (Gibbs et al., Proc. Natl. Acad. Sci. USA 86:6630-6634(1989)). Cytosol localized forms of Ras with normal GTPase activity do not act as inhibitors. Gibbs et al., ibid, showed this
25 effect in Xenopus oocytes and in mammalian cells.

Administration of compounds of the invention to block Ras farnesylation not only decreases the amount of Ras in the membrane but also generates a cytosolic pool of Ras. In tumor cells having activated
30 Ras, the cytosolic pool acts as another antagonist of membrane-bound Ras function. In normal cells having normal Ras, the cytosolic pool of Ras does not act as an antagonist. In the absence of complete inhibition of farnesylation, other farnesylated proteins are able to continue with their functions.

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Farnesyl-protein transferase activity may be reduced or completely inhibited by adjusting the compound dose. Reduction of farnesyl-protein transferase enzyme activity by adjusting the compound dose would be useful for avoiding possible undesirable side effects resulting from interference with other metabolic processes which utilize the enzyme.

These compounds and their analogs are inhibitors of farnesyl-protein transferase. Farnesyl-protein transferase utilizes farnesyl pyrophosphate to covalently modify the Cys thiol group of Ras, and other cellular proteins, with a farnesyl group. Inhibition of farnesyl pyrophosphate biosynthesis by inhibiting HMG-CoA reductase blocks Ras membrane localization in vivo and inhibits Ras function. Inhibition of farnesyl-protein transferase is more specific and is attended by fewer side effects than is the case for a general inhibitor of isoprene biosynthesis.

Previously, it has been demonstrated that tetrapeptides containing cysteine as an amino terminal residue with the CAAX sequence inhibit Ras farnesylation (Schaber et al., ibid; Reiss et al., ibid; Reiss et al., PNAS, 88:732-736 (1991)). It was, however, disclosed that tetrapeptides which further contained a cyclic amino acid residue, such as proline, had greatly reduced inhibitory activity when compared to tetrapeptides not containing a cyclic amino acid (Reiss et al., (1991)). Tetrapeptide inhibitors may inhibit while serving as alternate substrates for the Ras farnesyl-transferase enzyme, or may be purely competitive inhibitors (U.S. Patent 5,141,851, University of Texas).

Recently, it has been demonstrated that certain inhibitors of farnesyl-protein transferase selectively block the processing of Ras oncoprotein intracellularly (N.E. Kohl et al., Science, 260:1934-1937 (1993) and G.L. James et al., Science, 260:1937-1942 (1993)).

Among the inhibitors of farnesyl protein transferase that have been described in the art are benzodiazepine derivatives that mimic the CAAX motif of a prenylated protein (James, et al., Science, 1993, 260, 1937-1942). These compounds are potent inhibitors of FPTase. However, the compounds described by James, et al., are carboxylic

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acids which have relatively poor activity as inhibitors of farnesylation in intact cells. To render such compounds useful for inhibition of the transformed phenotype of a cancer cell, esterification of the C-terminal carboxylate is required. Such a prodrug strategy significantly
5 complicates the clinical application of an FPTase inhibitor by adding additional variables to its pharmacokinetic and pharmacodynamic behavior.

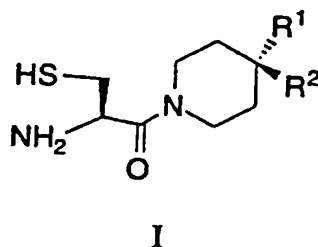
It is, therefore, an object of this invention to develop non-peptide compounds which will inhibit farnesyl-protein transferase and the farnesylation of the oncogene protein Ras. It is a further object
10 of this invention to develop chemotherapeutic compositions containing the compounds of this invention, and methods for producing the compounds of this invention.

It is also the object of the invention to provide a FPTase inhibitor which includes substituted piperidine analogs which inhibit
15 farnesyl-protein transferase and the farnesylation of the oncogene protein Ras p21, and chemotherapeutic compositions containing the compounds of this invention.

SUMMARY OF THE INVENTION

The present invention includes substituted piperidine analogs which inhibit farnesyl-protein transferase and the farnesylation
20 of the oncogene protein Ras p21. This invention also includes chemotherapeutic compositions containing the compounds of this invention, methods of inhibiting farnesyl-protein transferase and
25 methods for treating cancer.

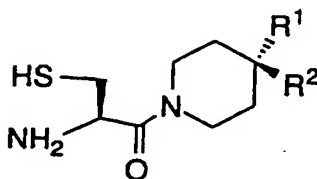
The compounds of this invention are illustrated by the Formula I:



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DETAILED DESCRIPTION OF THE INVENTION

The compounds of this invention are useful in the inhibition of farnesyl-protein transferase and the farnesylation of the oncogene protein Ras p21. In an embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by Formula I:



I

wherein:

R¹ is selected from:

- a) COR,
- b) CO₂R,
- c) CONHR,
- d) OH,
- e) OCOR,
- f) CN,
- g) CH₂OR,
- h) NHCOR,
- i) NHSO₂R, or
- j) COR⁵;

R is selected from:

- a) C₁₋₄ alkyl, unsubstituted or substituted with:
 - i) C₁₋₄ alkoxy,
 - ii) NR³R⁴,
 - iii) C₃₋₆ cycloalkyl,
 - iv) aryl or heterocycle; or
- b) aryl or heterocycle;

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R² is selected from: aryl, aralkyl, heterocycle, or heteroaralkyl, unsubstituted or substituted with one or more of:

- 5 a) C₁₋₄ alkyl, unsubstituted or substituted with:
- i) C₁₋₄ alkoxy,
- ii) NR³R⁴,
- iii) C₃₋₆ cycloalkyl, or
- iv) aryl or heterocycle;
- b) aryl or heterocycle,
- 10 c) halogen,
- d) OR³,
- e) NR³R⁴,
- f) CN,
- g) NO₂, or
- 15 h) CF₃;

R³ and R⁴ are independently selected from: H, C₁₋₄ alkyl, C₃₋₆ cycloalkyl, heterocycle, aryl, aroyl, heteroaryl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with one or more of:

- 20 a) C₁₋₄ alkoxy,
- b) aryl or heterocycle,
- c) halogen, or
- d) HO, wherein

25 or R³ and R⁴ may be joined in a ring;

R⁵ is selected from:

- a) a naturally occurring amino acid, or
- b) an oxidized form of a naturally occurring amino
- 30 acid which is:
- i) methionine sulfoxide, or
- ii) methionine sulfone;

or the pharmaceutically acceptable salt thereof.

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The preferred compounds of this invention are:

L-CysteinyI-4-(2-methylbenzyl)isonipecotyl-L-methionine;

5 L-CysteinyI-4-benzyl isonipecotic acid methyl ester;

L-CysteinyI-4-(2-methylbenzyl)isonipecotyl N-methyl amide;

10 L-CysteinyI-4-(2-methylbenzyl)isonipecotyl N-(2-pyridylmethyl)
amide;

L-CysteinyI-4-(2-methylbenzyl)isonipecotyl N-benzyl amide;

15 L-CysteinyI-4-(2-methylbenzyl)isonipecotic acid methyl ester;

L-CysteinyI-4-(2-chlorobenzyl)isonipecotic acid methyl ester;

L-CysteinyI-4-(2,3-dichlorobenzyl)isonipecotic acid methyl ester;

20 L-CysteinyI-4-(2,4-dichlorobenzyl)isonipecotic acid methyl ester;

L-CysteinyI-4-(2,6-dichlorobenzyl)isonipecotic acid methyl ester;

25 L-CysteinyI-4-(3-(2-methyl)pyridylmethyl)isonipecotic acid methyl
ester;

L-CysteinyI-4-(1-naphthyl)methyl isonipecotic acid methyl ester;

30 L-CysteinyI-4-(1-naphthyl)methyl isonipecotic acid ethyl ester;

L-CysteinyI-4-(1-naphthyl)methyl isonipecotic acid benzyl ester;

L-CysteinyI-4-(2-methylbenzyl)isonipecotic acid 2-pyridylmethyl
ester;

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L-Cysteiny-4-(2-methylbenzyl)isonipecotic acid 3-pyridylmethyl ester;

5 L-Cysteiny-4-(2-methylbenzyl)isonipecotic acid 4-pyridylmethyl ester;

L-Cysteiny-4-benzyl-4-piperidinol;

10 L-Cysteiny-4-acetoxy-4-benzylpiperidine;

L-Cysteiny-4-cyano-4-phenylpiperidine;

L-Cysteiny-4-acetyl-4-phenylpiperidine;

15 L-Cysteiny-4-methoxymethyl-4-(2-methylbenzyl)piperidine;

L-Cysteiny-4-acetamido-4-(2-methylbenzyl)piperidine;

20 L-Cysteiny-4-methylsulfonamido-4-(2-methylbenzyl)piperidine;

or the pharmaceutically acceptable salts thereof.

The more preferred compounds of this invention are:

25 L-Cysteiny-4-(2-methylbenzyl)isonipecotyl N-methyl amide;

L-Cysteiny-4-(2-methylbenzyl)isonipecotyl N-(2-pyridylmethyl) amide;

30 L-Cysteiny-4-(2-methylbenzyl)isonipecotyl N-benzyl amide;

L-Cysteiny-4-(2-methylbenzyl)isonipecotic acid methyl ester;

L-Cysteiny-4-(2-chlorobenzyl)isonipecotic acid methyl ester;

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L-Cysteiny-4-(2,3-dichlorobenzyl)isonipecotic acid methyl ester;

L-Cysteiny-4-(2,4-dichlorobenzyl)isonipecotic acid methyl ester;

5 L-Cysteiny-4-(2,6-dichlorobenzyl)isonipecotic acid methyl ester;

L-Cysteiny-4-(3-(2-methyl)pyridylmethyl)isonipecotic acid methyl ester;

10 L-Cysteiny-4-(1-naphthyl)methyl isonipecotic acid methyl ester;

L-Cysteiny-4-(1-naphthyl)methyl isonipecotic acid ethyl ester;

15 L-Cysteiny-4-(1-naphthyl)methyl isonipecotic acid benzyl ester;

L-Cysteiny-4-(2-methylbenzyl) isonipecotic acid 2-pyridylmethyl ester;

20 L-Cysteiny-4-(2-methylbenzyl) isonipecotic acid 3-pyridylmethyl ester;

L-Cysteiny-4-(2-methylbenzyl) isonipecotic acid 4-pyridylmethyl ester;

25 L-Cysteiny-4-benzyl-4-piperidinol;

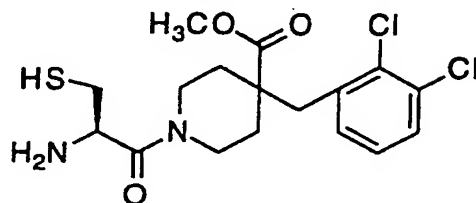
L-Cysteiny-4-methoxymethyl-4-(2-methylbenzyl)piperidine;

30 or the pharmaceutically acceptable salts thereof.

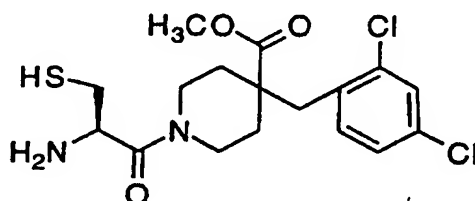
The most preferred compounds of this invention are:

- 10 -

L-Cysteinyl-4-(2,3-dichlorobenzyl)isonipecotic acid methyl ester;



L-Cysteinyl-4-(2,4-dichlorobenzyl)isonipecotic acid methyl ester;



or the pharmaceutically acceptable salts thereof.

As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms; "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge. "Halogen" or "halo" as used herein means fluoro, chloro, bromo and iodo.

As used herein, "aryl" is intended to mean any stable monocyclic, bicyclic or tricyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic. Examples of such aryl elements include phenyl, naphthyl, tetrahydronaphthyl, indanyl, biphenyl, phenanthryl, anthryl or acenaphthyl.

The term "aralkyl" represents a branched or straight-chain saturated aliphatic hydrocarbon groups having 1 to 4 carbon atoms, attached to any stable monocyclic, bicyclic or tricyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic.

The term heterocycle or heterocyclic, as used herein, represents a stable 5- to 7-membered monocyclic or stable 8- to 11-

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membered bicyclic or stable 11-15 membered tricyclic heterocyclic ring which is either saturated or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O, and S(O)_m (wherein m = 0, 1 or 2), and including
5 any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heterocyclic elements include, but are not
10 limited to, azepinyl, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnoliny, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, furyl, imidazolidinyl, imidazolinyl, imidazolyl, indoliny, indolyl, isochromanyl, isoindoliny, isoquinoliny,
15 isothiazolidinyl, isothiazolyl, isothiazolidinyl, morpholiny, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, 2-oxopiperazinyl, 2-oxopiperdinyl, 2-oxopyrrolidinyl, piperidyl, piperazinyl, pyridyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyrimidinyl, pyrrolidinyl, pyrrolyl, quinazolinyl, quinoliny, quinoxaliny, tetrahydrofuryl, tetrahydro-
20 isoquinoliny, tetrahydroquinoliny, thiamorpholiny, thiamorpholiny sulfoxide, thiazolyl, thiazolinyl, thienofuryl, thienothienyl, and thienyl.

The term "heteroaralkyl" is intended to mean a branched or straight-chain saturated aliphatic hydrocarbon groups having 1 to 4 carbon atoms, attached to a stable 5- to 7-membered monocyclic or
25 stable 8- to 11-membered bicyclic or stable 11-15 membered tricyclic heterocyclic ring which is either saturated or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O, and S(O)_m (wherein m = 0, 1 or 2), and including any bicyclic group in which any of the above-defined
30 heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure.

In the present invention, the term "naturally occurring amino acids" represents both the D and L enantiomer separately and

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the racemic mixture of the following amino acids, which may be identified both by conventional 3 letter and single letter abbreviations as indicated below:

5	Alanine	Ala	A
	Arginine	Arg	R
	Asparagine	Asn	N
	Aspartic acid	Asp	D
10	Asparagine or Aspartic acid	Asx	B
	Cysteine	Cys	C
	Glutamine	Gln	Q
	Glutamic acid	Glu	E
15	Glutamine or Glutamic acid	Glx	Z
	Glycine	Gly	G
	Histidine	His	H
	Isoleucine	Ile	I
20	Leucine	Leu	L
	Lysine	Lys	K
	Methionine	Met	M
	Phenylalanine	Phe	F
	Proline	Pro	P
	Serine	Ser	S
25	Threonine	Thr	T
	Tryptophan	Trp	W
	Tyrosine	Tyr	Y
	Valine	Val	V
30			

When R³ and R⁴ are joined, the cyclic amine substituent formed is a nitrogen containing ring, consisting of 4 to 6 members,

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optionally substituted with one of the following: O, S, or N. Examples of such cyclic amines include, but are not limited to: piperidine, piperazine, morpholine, azetidine, pyrrolidine, and thiazolidine.

5 The pharmaceutically acceptable salts of the compounds of this invention include the conventional non-toxic salts of the compounds of this invention as formed, e.g., from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like: and the salts prepared
10 from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pantoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxy-benzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic and the like.

15 The pharmaceutically acceptable salts of the compounds of this invention can be synthesized from the compounds of this invention which contain a basic moiety by conventional chemical methods. Generally, the salts are prepared by reacting the free base with stoichiometric amounts or with an excess of the desired salt-forming
20 inorganic or organic acid in a suitable solvent or various combinations of solvents.

The compounds of the invention can be synthesized by methods well known in the pharmaceutical arts, and the additional methods described below.

25 Abbreviations used in the description of the chemistry and in the Examples that follow are:

Ac ₂ O	Acetic anhydride;
Boc	t-Butoxycarbonyl;
30 BOP	Bis(2-oxo-3-oxazolidinyl)phosphonic chloride;
CBz	Benzyloxycarbonyl;
DMAP	4-Dimethylaminopyridine;
DMF	Dimethylformamide;
DPPA	Diphenylphosphoryl azide;

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	EDC	1-(3-Dimethylaminopropyl)-3-ethyl-carbodi-imide hydrochloride;
	HOBT	1-Hydroxybenzotriazole hydrate;
	Et ₃ N	Triethylamine;
5	EtOAc	Ethyl acetate;
	FAB	Fast atom bombardment;
	HOObt	3-Hydroxy-1,2,2-benzotriazin-4(3 <i>H</i>)-one;
	HPLC	High-performance liquid chromatography;
	KHMDS	Potassium bis(trimethylsilyl)amide;
10	MsCl	Methanesulfonyl chloride;
	NaHMDS	Sodium bis(trimethylsilyl)amide;
	Py	Pyridine;
	TFA	Trifluoroacetic acid;
	THF	Tetrahydrofuran;
15	Tr	Trityl, triphenylmethyl.

Synopsis of Reaction Schemes 1-8:

The compounds of this invention are prepared as illustrated by Reaction Schemes 1-8, in addition to other standard manipulations such as ester hydrolysis, cleavage of protecting groups, etc., as may be known in the literature or exemplified in the experimental procedures.

Specifically, Scheme 1 depicts the synthesis of the claimed amide analogs. The readily available N-Boc benzyl isonipecotate is alkylated by successive treatment with an amide base, such as lithium or sodium bis(trimethylsilyl)amide, or lithium diisopropylamide, followed by treatment with a 2-methyl benzyl halide. Hydrogenolysis of the benzyl ester, over a palladium on charcoal catalyst, furnishes the free carboxylic acid which is subsequently transformed into the amide by treatment with an amine or amine salt and an appropriate coupling reagent such as EDC. Boc deprotection of the piperidine nitrogen with anhydrous HCl provides the corresponding HCl salt which is coupled with the commercially available protected L-cysteine. Simultaneous amine and thiol deprotection with trifluoroacetic acid and triethylsilane, affords the claimed amide compounds.

- 15 -

The claimed ester analogs are prepared as illustrated in Scheme 2 by alkylating the readily available N-Boc isonipecotic acid esters with the appropriate benzyl halide in a manner similar to that described in Scheme 1. Subsequent coupling with the L-cysteine and simultaneous deprotection, also previously described, affords the ester analogs.

Scheme 3 depicts the preparation of the claimed pyridylmethyl esters which are achieved in a different sequence than those esters indicated in Scheme 2. In this sequence the N-Boc-4-(2-methylbenzyl)isonipecotic acid is converted to the pyridylmethyl ester with the corresponding pyridylmethyl carbinol and a coupling reagent such as EDC in combination with a catalytic amount of an activator such as DMAP. Subsequent cysteine coupling and deprotection as previously illustrated provides the pyridylmethyl ester analogs.

The 4-methoxymethylpiperidine analog is prepared via the route in Scheme 4. The benzyl ester of N-Boc 4-(2-methylbenzyl)isonipecotic acid is reduced with lithium aluminum hydride to the alcohol and then alkylated by treating the sodium salt with methyl iodide. The resulting methoxymethylpiperidine is deprotected, coupled with the L-cysteine and deprotected as previously described to afford the indicated methoxymethylpiperidine analog.

Scheme 5 shows the simple transformation of commercially available 4-cyano and 4-acetyl 4-phenyl piperidines to their products through previously described L-cysteine coupling and deprotection.

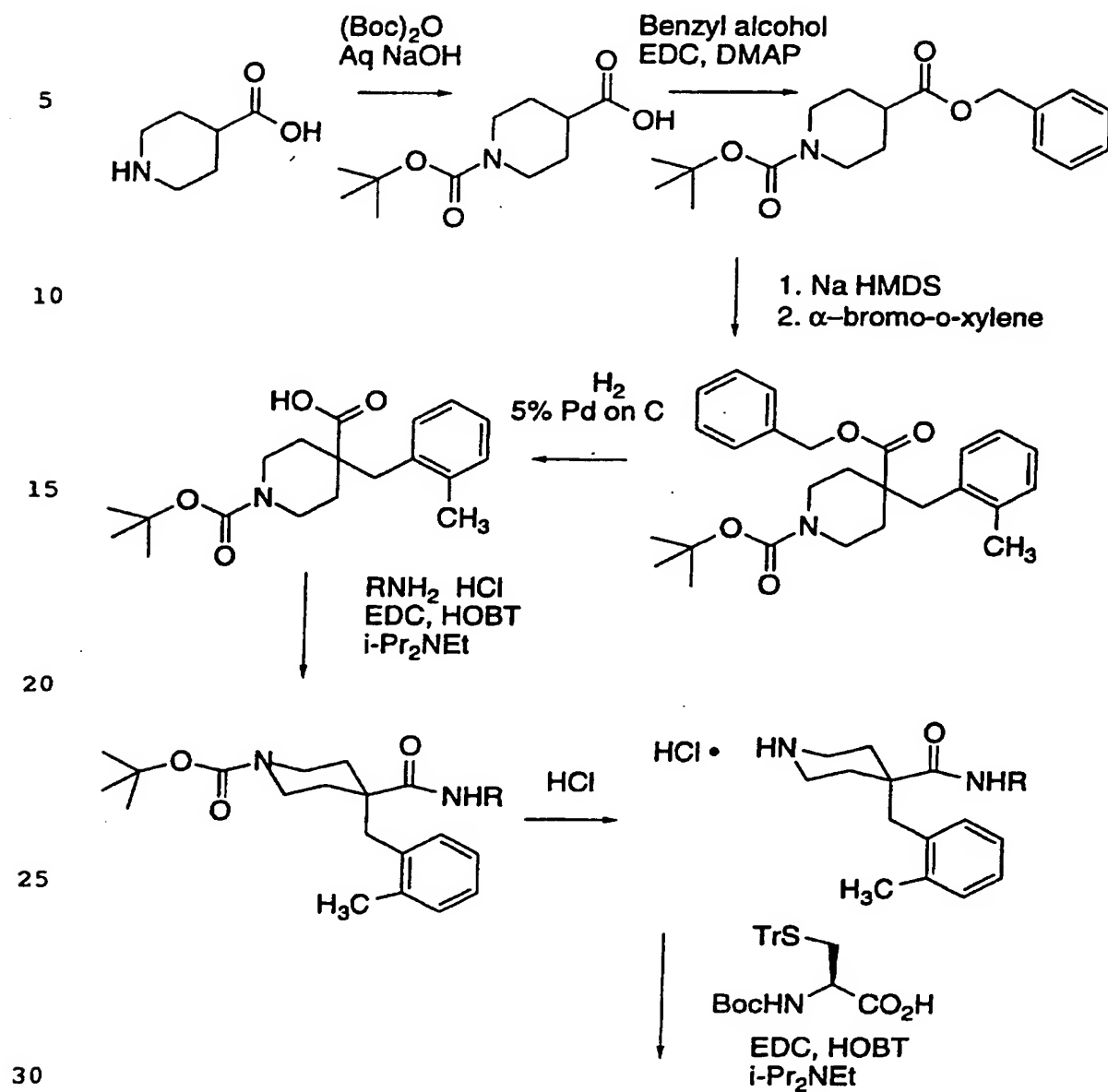
The hydroxypiperidine compound and its acetyl derivative are prepared as indicated in Scheme 6. Commercially available N-benzyl 4-piperidinone is treated with benzyl magnesium chloride to afford the benzyl alcohol. This compound is deprotected by hydrogenolysis over 10% palladium on charcoal catalyst to the free piperidine compound and then coupled to the protected L-cysteine in the previously indicated manner. The hydroxy compound is furnished by cysteine deprotection and its acetyl derivative by acetylation of the alcohol with acetic anhydride and a catalytic amount of DMAP followed by cysteine deprotection.

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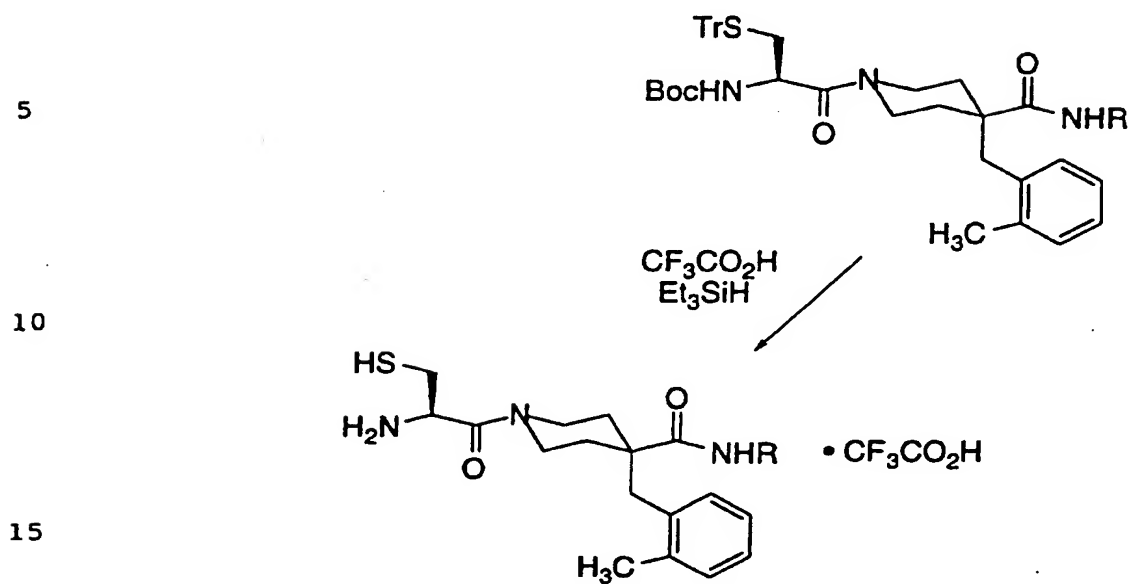
The synthesis of the claimed acetamido analog is depicted in Scheme 7. The protected 4-(2-methylbenzyl)isonipecotic acid undergoes a Curtius rearrangement by treatment with diphenylphosphoryl azide and triethylamine to afford the 4-aminopiperidine which is acetylated with acetic anhydride and then deprotected with anhydrous HCl. L-cysteine coupling and deprotection affords the indicated compound.

Preparation of the 4-methylsulfonylamido compound is shown in Scheme 8. The 4-amino-4-(2-methylbenzyl)piperidine is sulfonated with methane sulfonyl chloride, deprotected, coupled with the L-cysteine and a final deprotection affords the claimed compound.

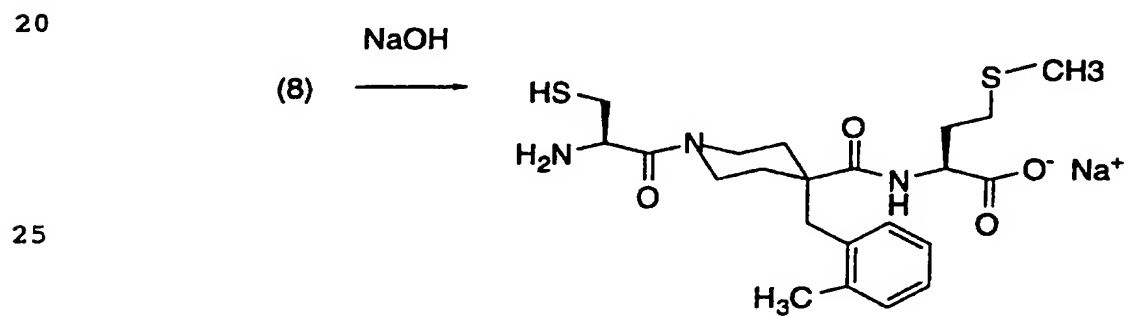
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REACTION SCHEME 1

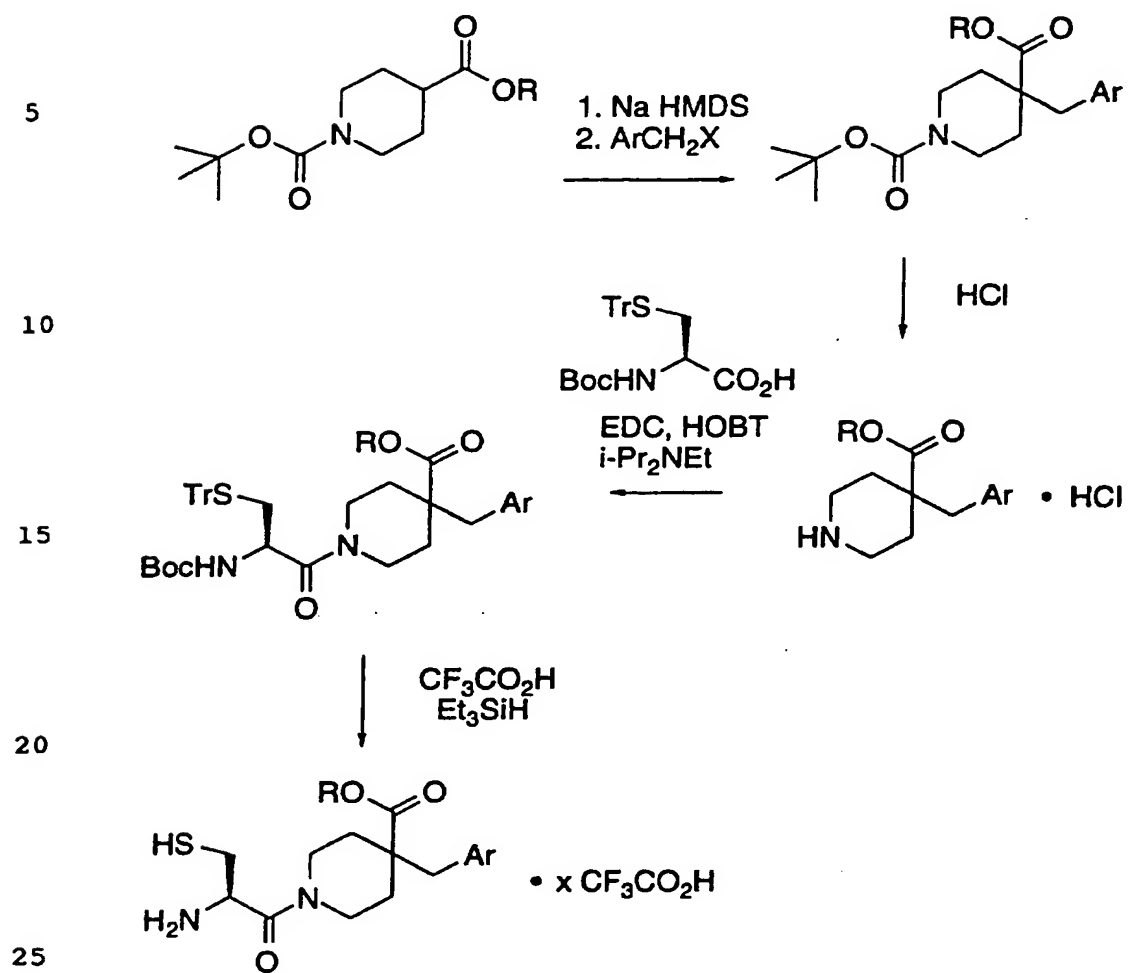
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REACTION SCHEME 1 (CONT'D.)

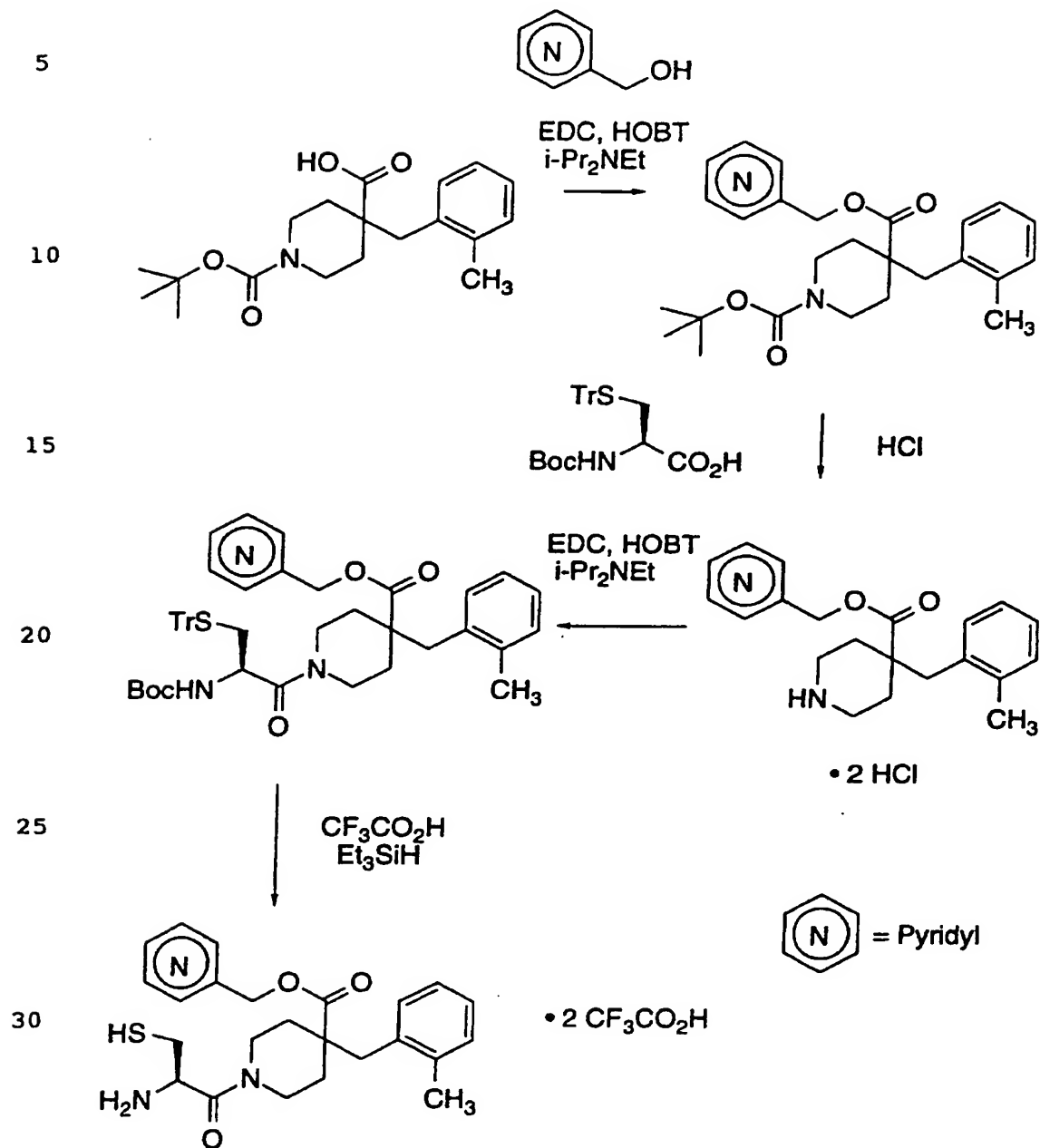
R = L-methionine methyl ester (8)



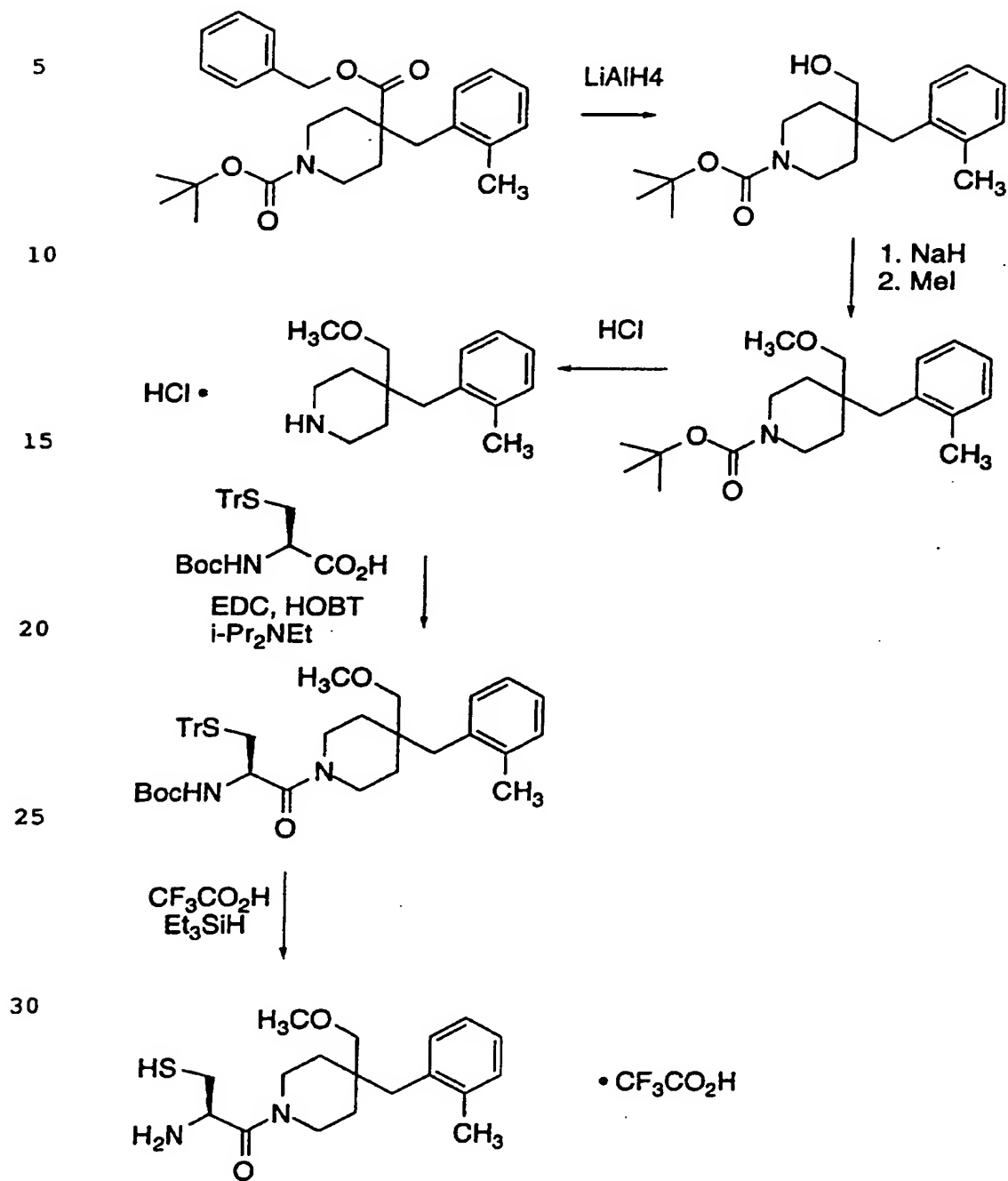
- 19 -

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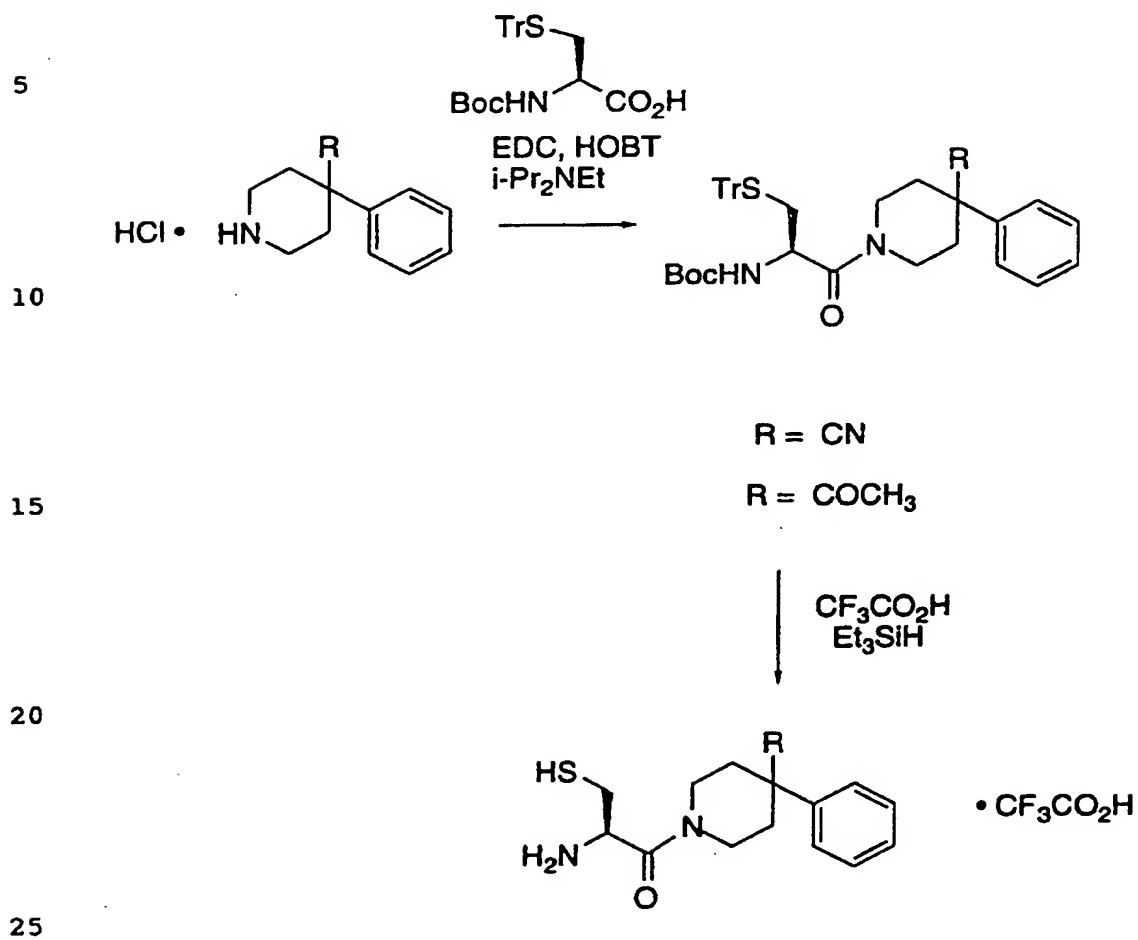
- 20 -

REACTION SCHEME 3

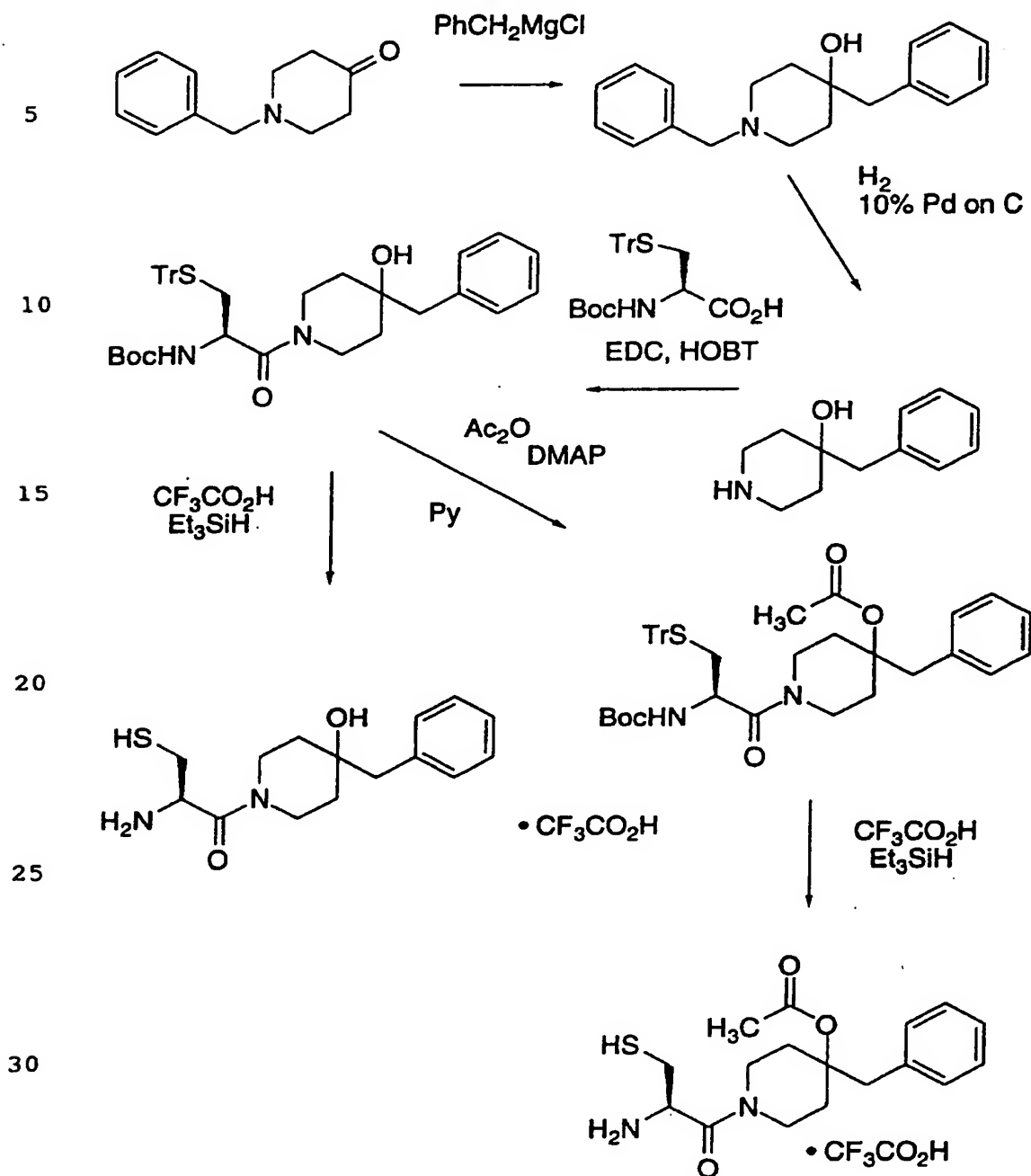
- 21 -

REACTION SCHEME 4

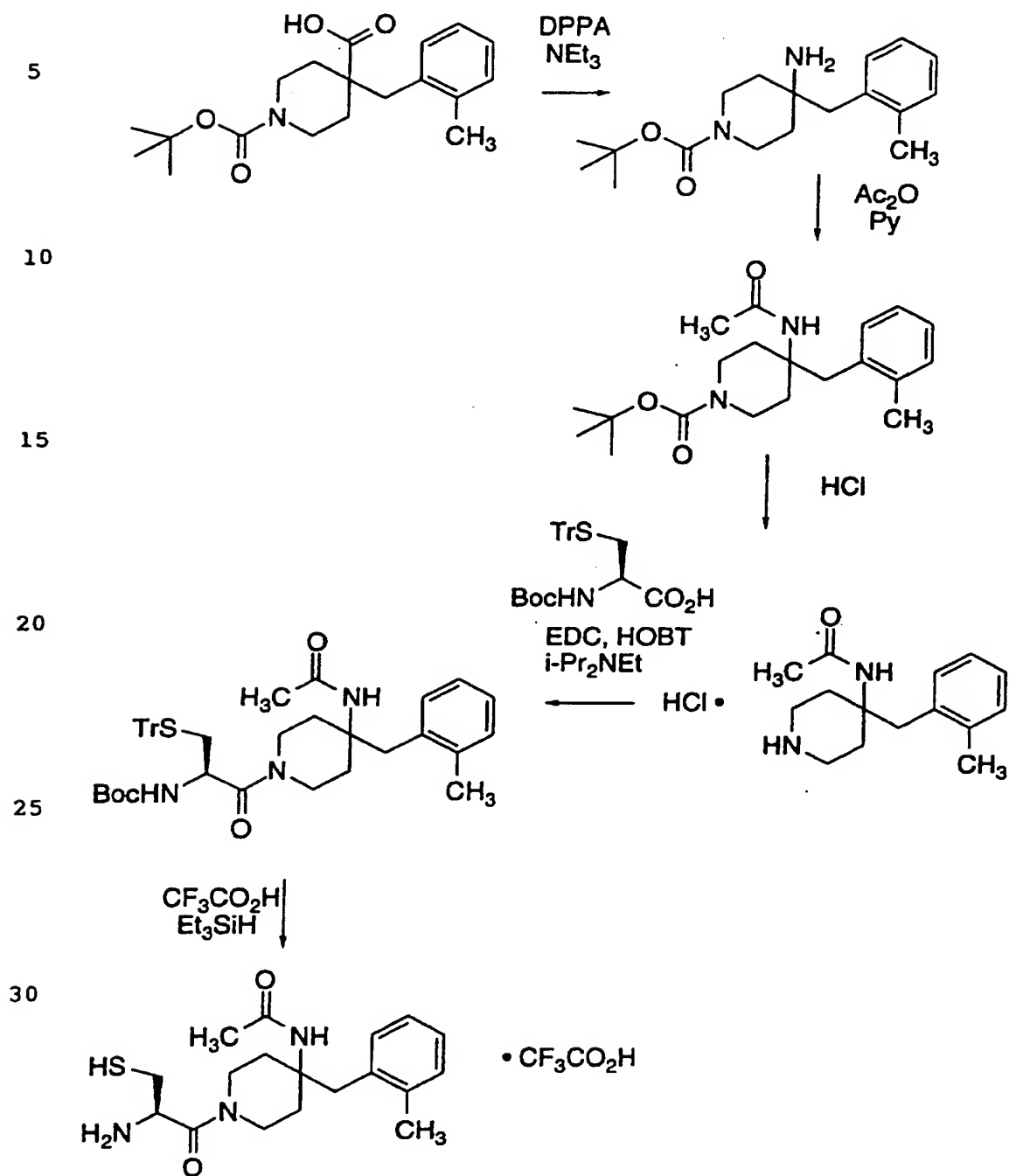
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REACTION SCHEME 5

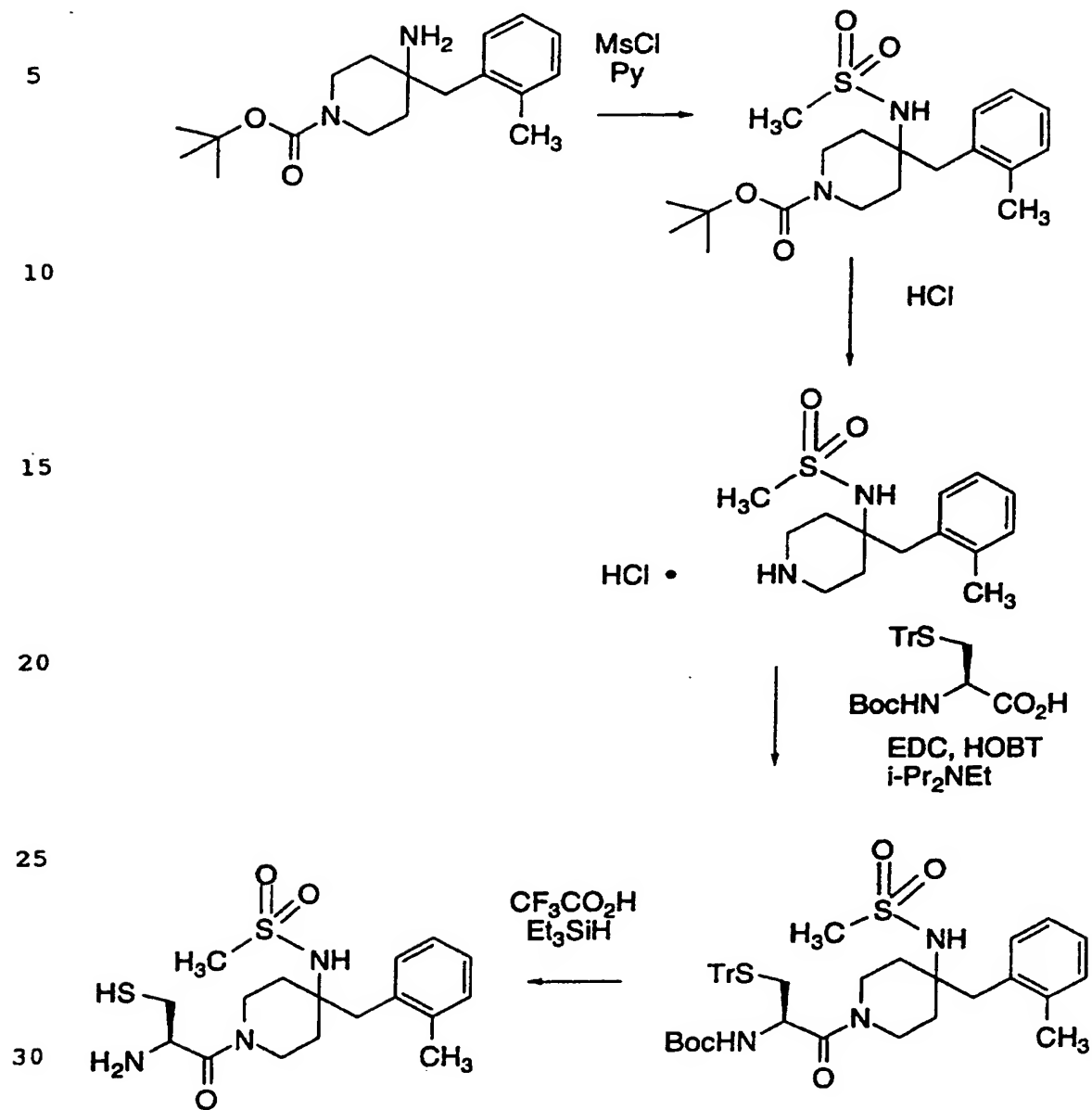
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REACTION SCHEME 6

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REACTION SCHEME 7

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REACTION SCHEME 8

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The compounds of this invention inhibit farnesyl-protein transferase and the farnesylation of the oncogene protein Ras. These compounds are useful as pharmaceutical agents for mammals, especially for humans. These compounds may be administered to patients for use
5 in the treatment of cancer. Examples of the type of cancer which may be treated with the compounds of this invention include, but are not limited to, colorectal carcinoma, exocrine pancreatic carcinoma, and myeloid leukemias.

The compounds of this invention may be administered to
10 mammals, preferably humans, either alone or, preferably, in combination with pharmaceutically acceptable carriers or diluents, optionally with known adjuvants, such as alum, in a pharmaceutical composition, according to standard pharmaceutical practice. The compounds can be administered orally or parenterally, including the
15 intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical routes of administration.

For oral use of a chemotherapeutic compound according to this invention, the selected compound may be administered, for
20 example, in the form of tablets or capsules, or as an aqueous solution or suspension. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch, and lubricating agents, such as magnesium stearate, are commonly added. For oral administration in capsule form, useful diluents include lactose and dried
25 corn starch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring agents may be added. For intramuscular, intraperitoneal, subcutaneous and intravenous use, sterile solutions of the active ingredient are usually prepared, and the
30 pH of the solutions should be suitably adjusted and buffered. For intravenous use, the total concentration of solutes should be controlled in order to render the preparation isotonic.

The present invention also encompasses a pharmaceutical composition useful in the treatment of cancer, comprising the administration of a therapeutically effective amount of the compounds

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of this invention, with or without pharmaceutically acceptable carriers or diluents. Suitable compositions of this invention include aqueous solutions comprising compounds of this invention and pharmacologically acceptable carriers, e.g., saline, at a pH level, e.g., 7.4. The solutions may be introduced into a patient's intramuscular blood-stream by local bolus injection.

When a compound according to this invention is administered into a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, and response of the individual patient, as well as the severity of the patient's symptoms.

In one exemplary application, a suitable amount of compound is administered to a mammal undergoing treatment for cancer. Administration occurs in an amount between about 0.1 mg/kg of body weight to about 60 mg/kg of body weight per day, preferably of between 0.5 mg/kg of body weight to about 40 mg/kg of body weight per day.

EXAMPLES

Examples provided are intended to assist in a further understanding of the invention. Particular materials, species and conditions employed are intended to be further illustrative of the invention and not limitative of the reasonable scope thereof.

EXAMPLE 1

L-Cysteinyl-4-(2-methylbenzyl)isonipecotyl-L-methionine

Step 1: Preparation of N-t-butoxycarbonyl isonipecotic acid

To a solution of isonipecotic acid (25.8 g, 200 mmol) in 1 M aqueous NaOH (223 ml, 223 mmol) was added a solution of di t-butyl dicarbonate in 200 ml THF over 1 hour. The resulting solution was stirred at room temp. overnight. The reaction mixture was then concentrated in vacuo to remove the THF and the residual aqueous

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solution extracted with hexane (2x125 ml). The hexane extracts were combined and back extracted with saturated NaHCO₃ (2x100 ml). All of the basic aqueous solutions were combined and cooled to 0°C and then acidified with a 15% aqueous KHSO₄ solution to a pH of 1-2. The resulting thick slurry was extracted with EtOAc (4x), combined and washed with brine, dried over MgSO₄ and concentrated in vacuo to afford the product as a white solid.

Step 2: Preparation of N-t-butoxycarbonyl isonipecotic acid benzyl ester

To a solution of N-t-butoxycarbonyl isonipecotic acid (12.0 g, 52.3 mmol) in 100 ml of anhydrous CH₂Cl₂, was added benzyl alcohol (6.0 ml, 58 mmol), followed by 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (11.04 g, 57.6 mmol), and 4-dimethylaminopyridine (642 mg, 5.25 mmol). The resulting mixture was stirred for 6 hours then diluted with CH₂Cl₂ (150 ml) and washed successively with H₂O, 10% aqueous citric acid, saturated NaHCO₃, brine and then dried over MgSO₄. Concentration in vacuo afforded a colorless oil which was chromatographed on silica with 20% EtOAc/hexane as eluent. Appropriate fractions were combined and concentrated in vacuo to afford the product as a white solid.

Step 3: Preparation of N-t-butoxycarbonyl-4-(2-methylbenzyl) isonipecotic acid benzyl ester

To a cold (-78°C) solution of N-t-butoxycarbonyl isonipecotic acid benzyl ester (13.34 g, 41.8 mmol) in 140 ml of dry THF was added a 1.0 M THF solution of sodium bis trimethylsilylamide (59 ml, 59 mmol) over 15 min. The resulting orange solution was stirred at -78°C for 1 h and then treated dropwise with α-bromo-o-xylene (6.8 ml, 50.7 mmol) and then allowed to warm slowly to room temp. overnight. The reaction was quenched with saturated aqueous NH₄Cl, diluted with H₂O, and extracted with EtOAc (2x). The combined organic extracts were washed with brine (2x), and concentrated in vacuo to an orange gum. Flash chromatography on

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Step 6: Preparation of 4-(2-methylbenzyl)isonipecotyl-L-methionine methyl ester HCl salt

A stream of anhydrous HCl gas was bubbled through a cold (0°C) solution of (N-t-butoxycarbonyl-4-(2-methylbenzyl) isonipe-
cotyl) L-methionine methyl ester (315 mg, 0.66 mmol) in 30 ml of
EtOAc for 10 min. and the reaction solution stirred 1 h more at 0°C.
The solution was then purged with argon for 10 min. and allowed to
warm to room temp. Concentration of the solution in vacuo afforded
the product as a colorless gum.

Step 7: Preparation of N-t-butoxycarbonyl-S-trityl-L-Cysteinyl-4-(2-methylbenzyl)isonipecotyl-L-methionine methyl ester

A solution of N-t-butoxycarbonyl-S-trityl-L-Cysteine (306
mg, 0.66 mmol), in 6 ml DMF under argon, was treated in succession
with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
(132 mg, 0.69 mmol), 1-hydroxybenzotriazole hydrate (93 mg, 0.69
mmol), HCl salt (280 mg, 0.67 mmol), and diisopropylethylamine (0.12
ml, 0.69 mmol). The resulting mixture was stirred at room temp.
overnight. The reaction solution was then concentrated in vacuo and
partitioned between EtOAc and H₂O. The EtOAc layer was then
washed with brine, dried over MgSO₄, and concentrated in vacuo to a
light brown gum. This material was then chromatographed on silica
with 40% EtOAc/hexane to afford, after combining and concentrating
the appropriate fractions, the product as a white foam.

Step 8: Preparation of L-Cysteinyl-4-(2-methylbenzyl)isoni-
pecotyl-L-methionine methyl ester trifluoroacetic acid salt

To a solution of methyl ester (75 mg, 0.09 mmol) in 2 ml
CH₂Cl₂, was added trifluoroacetic acid (1 ml) followed by triethyl-
silane (0.059 ml, 0.36 mmol). The solution was stirred for 1.5 h at
room temp. and then concentrated in vacuo. The residue was
partitioned between a 0.1% aqueous trifluoroacetic acid solution (5 ml)
and hexane. The aqueous layer was washed with hexane (4x) and then
concentrated in vacuo to a gum. This material was then purified by

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preparative HPLC on a VYDAC C¹⁸ protein and peptide column (22 mm diam.) and a 0.1% aqueous trifluoroacetic acid/CH₃CN mobile phase. The appropriate fractions were combined and lyophilized overnight to afford the product a white fluffy solid.

Anal. Calc'd for C₂₃H₃₅N₃O₄S₂ 1.30 CF₃CO₂H 0.25 H₂O:

C, 48.47; H, 5.85; N, 6.62.

Found: C, 48.49; H, 5.83; N, 6.83.

Step 9: Hydrolysis of Me ester

A 10 mmolar solution of the hydrolyzed methyl ester was generated in situ for enzyme assay by treating a solution of methionine methyl ester (3.9 mg, 6.15 micromol), in methanol (0.050 ml), with a 1.0 M aqueous NaOH solution (0.024 ml, 24 micromol). After agitating for 30 sec. and standing at room temp for 2 h the solution was diluted with methanol (0.540 ml) to afford a 10 mmolar solution of the sodium salt of the hydrolyzed ester. The hydrolysis was monitored by HPLC for completeness.

EXAMPLE 2

L-Cysteinyl-4-(2-methylbenzyl)isonipecotyl N-methyl amide
trifluoroacetic acid salt

Step 1: Preparation of N-t-butoxycarbonyl-4-(2-methylbenzyl)
isonipecotyl-N-methyl amide

A solution of N-t-butoxycarbonyl-4-(2-methylbenzyl) isonipecotic acid (167 mg, 0.50 mmol) in DMF (5 ml) was treated in succession with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (105 mg, 0.55 mmol), 1-hydroxybenzotriazole hydrate (75 mg, 0.56 mmol), methylamine hydrochloride (38 mg, 0.56 mmol), and diisopropylethylamine (0.097 ml, 0.56 mmol). The resulting mixture was stirred at room temp. overnight. The reaction solution was then concentrated in vacuo and partitioned between EtOAc and H₂O. The EtOAc layer was isolated and the aqueous layer extracted with

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EtOAc (2x). The EtOAc extracts were combined and washed with brine, dried over MgSO₄, and concentrated in vacuo to a light brown gum. This material was then chromatographed on silica with 40% EtOAc/hexane to afford, after combining and concentrating the appropriate fractions, the product as a colorless gum.

Step 2: Preparation of 4-(2-methylbenzyl)isonipecotyl-N-methyl amide hydrochloride salt

The N-t-butoxycarbonyl deprotection procedure as described above in Example 1, Step 6 was utilized to afford the product as a white solid.

Step 3: Preparation of N-t-butoxycarbonyl-S-trityl-L-Cysteinyl-4-(2-methylbenzyl)isonipecotyl-N-methyl amide

The coupling procedure as described above in Example 1, Step 7 was utilized to afford the product as a white foam.

Step 4: Preparation of L-Cysteinyl-4-(2-methylbenzyl)isonipecotyl-N-methyl amide trifluoroacetic acid salt

Cysteine deprotection as described above in Example 1, Step 8 afforded the product as a white fluffy solid.

Anal. Calc'd for C₁₈H₂₇N₃O₂S 1.25 CF₃CO₂H 0.45 H₂O:

C, 49.23; H, 5.87; N, 8.40.

Found: C, 49.25; H, 5.87; N, 8.46.

EXAMPLE 3

L-Cysteinyl-4-(2-methylbenzyl)isonipecotyl N-(2-pyridylmethyl) amide trifluoroacetic acid salt

The titled compounds were prepared according to the methods of Example 2, substituting (2-aminomethyl) pyridine in Step 1. The amide bis trifluoroacetic acid salt was obtained as a white fluffy solid.

Anal. Calc'd for C₂₃H₃₀N₄O₂S 2.25 CF₃CO₂H 0.65 H₂O:

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Found: C, 47.54; H, 4.87; N, 8.06.
C, 47.50; H, 4.87; N, 8.09.

EXAMPLE 4

L-Cysteiny-4-(2-methylbenzyl)isonipecotyl N-benzyl amide
trifluoroacetic acid salt

The titled compounds were prepared according to the methods of Example 2, substituting benzylamine in Step 1. The amide trifluoroacetic acid salt was obtained as a white fluffy solid.

Anal. Calc'd for $C_{24}H_{31}N_3O_2S \cdot 1.30 CF_3CO_2H \cdot 0.50 H_2O$:

C, 54.82; H, 5.76; N, 7.21.

Found: C, 54.83; H, 5.72; N, 7.30.

EXAMPLE 5

L-Cysteiny-4-(2-methylbenzyl)isonipecotic acid methyl ester
trifluoroacetic acid salt

Step 1: Preparation of N-t-butoxycarbonyl isonipecotic acid methyl ester

To an ice cold solution of N-t-butoxycarbonyl isonipecotic acid (8.8 g, 34.9 mmol), in a 10% mixture of methanol in benzene (250 ml), was added a 2.0 M solution of trimethylsilyldiazomethane in hexanes, dropwise, until a consistent yellow color was obtained (~30 ml). After vigorous gas evolution had ceased, cooling was removed and the reaction mixture stirred for 1 h at room temperature. The mixture was then treated dropwise with glacial acetic acid until all yellow color had dissipated. It was then stirred 15 min. and concentrated in vacuo to a pale yellow oil. This material was purified by column chromatography on silica with 20% EtOAc/hexane as eluent. The appropriate fractions were combined and concentrated in vacuo to afford the product as a colorless oil.

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Step 2: Preparation of N-t-butoxycarbonyl-4-(2-methylbenzyl)-isonipecotic acid methyl ester

N-t-butoxycarbonyl isonipecotic acid methyl ester was transformed utilizing the alkylation procedure as described in Example 1, Step 3 substituting lithium diisopropylamide as the base to afford the product as a yellow syrup.

Step 3: Preparation of 4-(2-methylbenzyl)isonipecotic acid methyl ester HCl salt

4-(2-methylbenzyl) N-t-butoxycarbonyl isonipecotic acid methyl ester was deprotected as described above in Example 1, Step 6 to afford the product as a white solid.

Step 4: Preparation of N-t-butoxycarbonyl-S-trityl-L-Cysteiny-4-(2-methylbenzyl)isonipecotic acid methyl ester

The HCl salt was coupled to N-t-butoxycarbonyl-S-trityl-L-Cysteine utilizing the procedure described in Example 1, Step 7 to afford the product as a white foam.

Step 5: Preparation of L-Cysteiny-4-(2-methylbenzyl)isonipecotic acid methyl ester Trifluoroacetic acid salt

The methyl ester was deprotected and purified as described in Example 1, Step 8 to afford the product as a white fluffy solid.

Anal. Calc'd for $C_{23}H_{35}N_3O_4S_2 \cdot 1.30 CF_3CO_2H \cdot 0.25 H_2O$:

C, 49.17; H, 5.57; N, 5.57.

Found: C, 49.16; H, 5.55; N, 5.80.

EXAMPLE 6

L-Cysteiny-4-benzyl isonipecotic acid methyl ester trifluoroacetic acid salt

The titled compounds were prepared according to the methods of Example 4, substituting benzyl bromide in Step 2. The

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methyl ester trifluoroacetic acid salt was obtained as a white fluffy solid.

Anal. Calc'd for $C_{17}H_{24}N_2O_3S \cdot 1.20 CF_3CO_2H$:

C, 49.23; H, 5.37; N, 5.92.

Found: C, 48.91; H, 5.28; N, 5.94.

EXAMPLE 7

L-Cysteinyl-4-(2-chlorobenzyl)isonipecotic acid methyl ester
trifluoroacetic acid salt

The titled compounds were prepared according to the methods of Example 4, substituting 2-chlorobenzyl bromide in Step 2. The methyl ester trifluoroacetic acid salt was obtained as a white fluffy solid.

Anal. Calc'd for $C_{17}H_{23}ClN_2O_3S \cdot 1.40 CF_3CO_2H$:

C, 44.83; H, 4.64; N, 5.28.

Found: C, 44.64; H, 4.66; N, 5.30.

EXAMPLE 8

L-Cysteinyl-4-(2,3-dichlorobenzyl)isonipecotic acid methyl ester
trifluoroacetic acid salt

The titled compounds were prepared according to the methods of Example 4, substituting 2,3-dichlorobenzyl bromide (prepared from 2,3-dichlorotoluene according to the procedure described in J. Chem. Res. (S) (1984) 24.) in Step 2. The methyl ester trifluoroacetic acid salt was obtained as a white solid.

Anal. Calc'd for $C_{17}H_{22}N_2O_3S \cdot 1.55 CF_3CO_2H \cdot 0.15 H_2O$:

C, 41.28; H, 4.11; N, 4.79.

Found: C, 41.26; H, 4.09; N, 5.11.

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EXAMPLE 9

L-Cysteinyl-4-(2,4-dichlorobenzyl)isonipecotic acid methyl ester
trifluoroacetic acid salt

5 The titled compounds were prepared according to the
methods of Example 4, substituting α , 2,4-trichlorotoluene in Step 2.
The methyl ester trifluoroacetic acid salt was obtained as a white solid.
Anal. Calc'd for $C_{17}H_{22}N_2O_3S \cdot 1.55 CF_3CO_2H$:
C, 41.48; H, 4.08; N, 4.81.
10 Found: C, 41.51; H, 4.08; N, 4.98.

EXAMPLE 10

15 L-Cysteinyl-4-(2,6-dichlorobenzyl)isonipecotic acid methyl ester
trifluoroacetic acid salt

 The titled compounds were prepared according to the
methods of Example 4, substituting α , 2,6-trichlorotoluene in Step 2.
The methyl ester trifluoroacetic acid salt was obtained as a white fluffy
solid.
20 Anal. Calc'd for $C_{17}H_{22}N_2O_3S \cdot 1.25 CF_3CO_2H \cdot 0.15 H_2O$:
C, 42.54; H, 4.31; N, 5.09.
Found: C, 42.55; H, 4.30; N, 5.11.

EXAMPLE 11

25 L-Cysteinyl-4-(3-(2-methyl)pyridylmethyl)isonipecotic acid methyl
ester trifluoroacetic acid salt

 The titled compounds were prepared according to the
methods of Example 4, substituting 3-(chloromethyl)-2-methyl pyridine
30 (preparation described below). The methyl ester bis trifluoroacetic acid
salt was obtained as a colorless gum.
Anal. Calc'd for $C_{17}H_{25}N_3O_3S \cdot 1.45 CF_3CO_2H \cdot 0.30 H_2O$:
C, 41.34; H, 4.44; N, 6.60.
Found: C, 41.33; H, 4.44; N, 6.74.

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Preparation of 3-(Chloromethyl)-2-methyl pyridineStep 1: Preparation of 3-hydroxymethyl-2-methylpyridine

To a suspension of lithium aluminum hydride (2.0 g, 53 mmol) in anhydrous ether (300 ml) was added a solution of methyl-2-methylpyridine carboxylate (8.14 g, 53.8 mmol) in 100 ml anhydrous ether over 20 min. The reaction mixture was stirred 1.5 h at room temp. and the treated carefully in succession with 2 ml of water, 2 ml of 15% aqueous sodium hydroxide, and 6 ml of water. The white slurry was stirred 1 h at room temp. and then filtered through Celite. After several washings with ether, the combined filtrates were washed with brine, dried (MgSO₄), and concentrated in vacuo to a pale yellow oil. This material was purified by column chromatography on silica with 5% methanol/chloroform as eluent to afford the product as a colorless oil.

Step 2: Preparation of 3-chloromethyl-2-methylpyridine

To a solution of 3-hydroxymethyl-2-methylpyridine (0.65 g, 5.3 mmol) in dry benzene (5 ml) was added triethylamine (1.0 ml, 7.4 mmol) followed by methanesulfonyl chloride (0.78 ml, 10.1 mmol) dropwise over 5 min. The heterogeneous dark gummy mixture was stirred at room temp. overnight. The reaction was filtered through Celite and washed with benzene (2x). The combined filtrates were washed with brine, dried (Na₂SO₄), and concentrated in vacuo to the crude product as a yellow oil which was used as is.

EXAMPLE 12L-Cysteinyl-4-(1-naphthyl)methyl isonipecotic acid methyl ester trifluoroacetic acid salt

The titled compounds were prepared according to the methods of Example 4, substituting 1-(bromomethyl) naphthalene (preparation described below) and lithium diisopropylamide as the base

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in Step 2. The methyl ester trifluoroacetic acid salt was obtained as a white fluffy solid.

Anal. Calc'd for $C_{21}H_{26}N_2O_3S \cdot 1.25 CF_3CO_2H \cdot 0.95 H_2O$:

C, 51.68; H, 5.38; N, 5.13.

Found: C, 51.64; H, 5.43; N, 5.14.

Preparation of 1-(bromomethyl) naphthalene

To a suspension of triphenylphosphine (10.5 g, 40 mmol) and carbon tetrabromide (13.3 g, 40 mmol) in anhydrous ether (200 ml) was added 1-naphthylmethanol (5.28 g, 33.4 mmol). The mixture was stirred at room temp. for 2 h and then concentrated in vacuo to a pale orange oil. This material was triturated with hexane and the resulting pale orange solid removed via filtration. The solid was washed several times with hexane and the combined filtrates from the washings passed through a short column of Florisil. Concentration in vacuo of the eluent afforded the bromide as a pale yellow solid.

EXAMPLE 13

L-Cysteinyl-4-(1-naphthyl)methyl isonipecotic acid ethyl ester
trifluoroacetic acid salt

The titled compounds were prepared according to the methods of Example 4, utilizing N-t-butoxycarbonyl isonipecotic acid ethyl ester and alkylating with 1-(bromomethyl) naphthalene and lithium diisopropylamide as the base in Step 2. The ethyl ester trifluoroacetic acid salt was obtained as a white fluffy solid.

Anal. Calc'd for $C_{22}H_{28}N_2O_3S \cdot 1.05 CF_3CO_2H \cdot 0.25 H_2O$:

C, 55.16; H, 5.68; N, 5.34.

Found: C, 55.13; H, 5.72; N, 5.20.

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EXAMPLE 14L-Cysteinyl-4-(1-naphthyl)methyl isonipecotic acid benzyl ester
trifluoroacetic acid salt

The titled compounds were prepared according to the methods of Example 4, utilizing N-t-butoxycarbonyl isonipecotic acid benzyl ester and alkylating with 1-(bromomethyl) naphthalene and lithium diisopropylamide as the base in Step 2. The benzyl ester trifluoroacetic acid salt was obtained as a white fluffy solid.

Anal. Calc'd for C₂₇H₃₀N₂O₃S 1.30 CF₃CO₂H:

C, 58.20; H, 5.16; N, 4.59.

Found: C, 58.25; H, 5.18; N, 4.94.

EXAMPLE 15L-Cysteinyl-4-(2-methylbenzyl)isonipecotic acid 2-pyridylmethyl
ester trifluoroacetic acid saltStep 1: Preparation of N-t-butoxycarbonyl-4-(2-methylbenzyl)
isonipecotic acid 2-pyridylmethyl ester

To a solution of N-t-butoxycarbonyl-4-(2-methylbenzyl) isonipecotic acid (666 mg, 2.0 mmol) in dry CH₂Cl₂ (15 ml) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (421 mg, 2.2 mmol). After stirring 15 min., 2-pyridine carbinol (0.21 ml, 2.2 mmol) and 4-dimethylaminopyridine (244 mg, 2.0 mmol) were added and the reaction mixture stirred at room temp. overnight. The reaction mixture was then adsorbed directly onto a small amount of silica and chromatographed with 30% EtOAc/hexane as eluent. The appropriate fractions were combined and concentrated in vacuo to afford the product as a colorless gum.

Step 2: Preparation of 4-(2-methylbenzyl)isonipecotic acid 2-
pyridylmethyl ester bis HCl salt

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N-t-butoxycarbonyl-4-(2-methylbenzyl)isonipecotic acid 2-pyridylmethyl ester was deprotected as described above in Example 1, Step 6 to afford the product as a white hygroscopic solid.

5 Step 3: Preparation of N-t-butoxycarbonyl-S-trityl-L-Cysteinyl-
 4-(2-methylbenzyl)isonipecotic acid 2-pyridylmethyl ester
 4-(2-methylbenzyl)isonipecotic acid 2-pyridylmethyl ester
 bis HCl salt was coupled to N-t-butoxycarbonyl-S-trityl-L-Cysteine
10 utilizing the procedure described in Example 1, Step 7 to afford the
 product as a white foam.

Step 4: Preparation of L-Cysteinyl-4-(2-methylbenzyl)isoni-
 pecotic acid 2-pyridylmethyl ester bis trifluoroacetic acid
 salt
15 N-t-butoxycarbonyl-S-trityl-L-Cysteine 4-(2-methyl-
 benzyl)isonipecotic acid 2-pyridylmethyl ester was deprotected and
 purified as described in Example 1, Step 8 to afford the product as a
 white fluffy solid.
20 Anal. Calc'd for C₂₃H₂₉N₃O₃S 2.80 CF₃CO₂H 0.20 H₂O:
 C, 45.78; H, 4.33; N, 5.60.
 Found: C, 45.78; H, 4.33; N, 5.87.

EXAMPLE 15(a)

25 L-Cysteinyl-4-(2-methylbenzyl)isonipecotic acid 3-pyridylmethyl
 ester trifluoroacetic acid salt

 The titled compounds were prepared according to the
 methods of Example 15, substituting 3-pyridine carbinol. The methyl
 ester bis trifluoroacetic acid salt was obtained.
30 Anal. Calc'd for C₂₃H₂₉N₃O₃S 2.35 CF₃CO₂H 0.40 H₂O:
 C, 47.35; H, 4.61; N, 5.98.
 Found: C, 47.33; H, 4.63; N, 6.06.

EXAMPLE 15(b)

5 L-Cysteinyl-4-(2-methylbenzyl)isonipecotic acid 4-pyridylmethyl
ester trifluoroacetic acid salt

The titled compounds were prepared according to the methods of Example 15, substituting 4-pyridine carbinol. The methyl ester bis trifluoroacetic acid salt was obtained.

Anal. Calc'd for C₂₃H₂₉N₃O₃S 2.10 CF₃CO₂H 1.70 H₂O:

10 C, 46.83; H, 4.98; N, 6.02.

Found: C, 46.83; H, 5.02; N, 6.03.

EXAMPLE 16

15 L-Cysteinyl-4-benzyl-4-piperidinol trifluoroacetic acid salt

Step 1: Preparation of N-benzyl-4-benzyl-4-piperidinol

To a solution of benzyl magnesium chloride (40 ml of 2.0 M soln. in THF, 80 mmol) in THF (80 ml) was added 1-benzyl-4-piperidinone (7.4 ml, 40 mmol) over 7 min. and stirred overnight. The
20 reaction mixture was poured over ice and extracted with ether (2x). The combined ether extracts were washed with brine, dried (Na₂SO₄), and concentrated in vacuo to a pale green syrup. This material was chromatographed on silica with 50-60% EtOAc/hexane as eluent. The
25 appropriate fractions were combined and concentrated in vacuo to afford the product as an off white solid.

Step 2: Preparation of 4-Benzyl-4-piperidinol

A mixture of N-benzyl-4-benzyl-4-piperidinol (2.0 g, 7.1 mmol) and 10% palladium on charcoal catalyst (0.5 g) in absolute
30 ethanol (100 ml), was stirred vigorously at 40°C under a balloon of hydrogen for 5 h. The reaction mixture was then filtered through a pad of Celite and the filtrate concentrated in vacuo to a grayish solid. This material was dissolved in methanol and filtered a second time through

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Celite and the filtrate concentrated in vacuo to the product, a white solid.

5 Step 3: Preparation of N-t-butoxycarbonyl-S-trityl-L-Cysteinyl-4-benzyl-4-piperidinol

The coupling procedure as described above in Example 1, Step 7 was utilized, with the amendment that no amine base was added, to afford the product as a white foam.

10 Step 4: Preparation of L-Cysteinyl-4-benzyl-4-piperidinol

Cysteine deprotection as described above in Example 1, Step 8 afforded the product as a white solid.

Anal. Calc'd for C₁₅H₂₂N₂O₂S 1.30 CF₃CO₂H 0.05 H₂O:

C, 47.66; H, 5.32; N, 6.32.

15 Found: C, 47.68; H, 5.32; N, 6.32.

EXAMPLE 17

20 L-Cysteinyl-4-acetoxy-4-benzylpiperidine trifluoroacetic acid salt

Step 1: Preparation of N-t-butoxycarbonyl-S-trityl-L-Cysteine-4-acetoxy-4-benzylpiperidine

25 To a solution of N-t-butoxycarbonyl-S-trityl-L-Cysteinyl-4-benzyl-4-piperidinol (100 mg, 0.16 mmol) in dry pyridine (2 ml), was added 4-dimethylaminopyridine (25 mg, 0.20 mmol) and acetic anhydride (0.030 ml, 0.32 mmol). The solution was heated to 50°C (oil bath temp.) for 2 days and then allowed to cool to room temp. The reaction mixture was concentrated in vacuo and the residue partitioned between EtOAc and brine. The EtOAc layer was dried (MgSO₄) and
30 concentrated in vacuo to a brown oil. This material was purified by column chromatography on silica with 18-20% EtOAc/hexane as eluent. The appropriate fractions were combined and concentrated in vacuo to afford the product as a glassy solid.

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Step 2: Preparation of L-Cysteinyl-4-acetoxy-4-benzylpiperidine

Cysteine deprotection as described above in Example 1,

Step 8 afforded the product as a white fluffy solid.

Anal. Calc'd for $C_{17}H_{24}N_2O_3S \cdot 1.15 CF_3CO_2H \cdot 0.40 H_2O$:

5 C, 48.73; H, 5.52; N, 5.89.

Found: C, 48.75; H, 5.48; N, 6.16.

EXAMPLE 1810 L-Cysteinyl-4-cyano-4-phenylpiperidine trifluoroacetic acid saltStep 1: Preparation of N-t-butoxycarbonyl-S-trityl-L-Cysteinyl-4-cyano-4-phenylpiperidine

The coupling procedure as described above in Example 1,

15 Step 7 was utilized, with commercially available 4-phenyl-4-cyano-piperidine hydrochloride salt, to afford the product as a white foam.

Step 2: Preparation of L-Cysteinyl-4-cyano 4-phenylpiperidine

Cysteine deprotection as described above in Example 1,

20 Step 8 afforded the product as a white solid.

Anal. Calc'd for $C_{15}H_{19}N_3OS \cdot 1.20 CF_3CO_2H \cdot 0.15 H_2O$:

C, 48.72; H, 4.82; N, 9.80.

Found: C, 48.78; H, 4.81; N, 9.75.

25 EXAMPLE 19L-Cysteinyl-4-acetyl-4-phenylpiperidine trifluoroacetic acid salt30 Step 1: Preparation of N-t-butoxycarbonyl-S-trityl-L-Cysteinyl-4-acetyl-4-phenylpiperidine

The coupling procedure as described above in Example 1,

Step 7 was utilized, with commercially available 4-acetyl-4-phenyl-piperidine hydrochloride salt, to afford the product as a white foam.

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Step 2: Preparation of L-Cysteinyl-4-acetyl-4-phenylpiperidine

Cysteine deprotection as described above in Example 1, Step 8 afforded the product as a white solid.

Anal. Calc'd for $C_{16}H_{22}N_2O_2S \cdot 1.45 CF_3CO_2H$:

C, 48.12; H, 5.01; N, 5.94.

Found: C, 48.02; H, 5.06; N, 5.96.

EXAMPLE 20

L-Cysteinyl-4-methoxymethyl-4-(2-methylbenzyl)piperidine trifluoroacetic acid salt

Step 2: Preparation of N-t-Butoxycarbonyl-4-hydroxymethyl-4-(2-methylbenzyl)piperidine

To a suspension of lithium aluminum hydride (0.32 g, 8.4 mmol) in anhydrous ether (50 ml) was added a solution of 4-(2-methylbenzyl) N-t-butoxycarbonyl isonipecotic acid benzyl ester (3.0 g, 7.1 mmol) in anhydrous ether (25 ml) over 15 min. The resulting mixture was heated gently at reflux for 1 h. The reaction mixture was then quenched with the slow and successive addition of H_2O (0.32 ml), 15% aqueous NaOH, and H_2O (0.96 ml). After stirring for 30 min., the mixture was filtered through Celite and the filtrate washed with brine, dried ($MgSO_4$), and concentrated in vacuo to a colorless syrup.

Purification by column chromatography on silica with 25%-50% EtOAc/hexane as eluent afforded the product as a colorless gum. This material was recrystallized from EtOAc and hexane to afford a white solid. m.p. 104-106°C.

Step 2: Preparation of N-t-Butoxycarbonyl-4-methoxymethyl-4-(2-methylbenzyl)piperidine

To a 0°C suspension of sodium hydride (19 mg, 0.80 mmol) in 1.5 ml of THF, was added a solution of N-t-butoxycarbonyl-4-hydroxymethyl-4-(2-methylbenzyl)piperidine (200 mg, 0.63 mmol) in 1 ml THF. The mixture was allowed to warm to room temp. To this

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suspension was added 0.35 ml of anhydrous DMSO and the mixture was heated to 60°C and stirred 5 h until the solution was almost homogeneous. The reaction mixture was allowed to cool to room temp. and to this solution was added methyl iodide (0.070 ml, 1.12 mmol). The resulting heterogeneous mixture was stirred at room temp. overnight. The reaction mixture was treated with 10% aqueous citric acid and extracted with ether (3x). The combined ether extracts were washed successively with saturated aqueous NaHCO₃ and brine, dried (MgSO₄), and concentrated in vacuo to a yellow gum. Purification by column chromatography on silica with 9% EtOAc/hexane as eluent afforded the product as a colorless gum.

Step 2: Preparation of 4-Methoxymethyl-4-(2-methylbenzyl)-piperidine HCl salt

N-t-Butoxycarbonyl-4-methoxymethyl-4-(2-methylbenzyl)piperidine was deprotected as described above in Example 1, Step 6 to afford the product as a white solid.

Step 3: Preparation of N-t-butoxycarbonyl-S-trityl-L-Cysteinyl-4-methoxymethyl-4-(2-methylbenzyl)piperidine

The coupling procedure as described above in Example 1, Step 7 was utilized to afford the product as a white foam.

Step 4: Preparation of L-Cysteinyl-4-methoxymethyl-4-(2-methylbenzyl)piperidine

Cysteine deprotection as described above in Example 1, Step 8 afforded the product as a white solid.

Anal. Calc'd for C₁₈H₂₈N₂O₂S 1.25 CF₃CO₂H 0.20 H₂O:

C, 51.02; H, 6.19; N, 5.80.

Found: C, 50.97; H, 6.19; N, 6.04.

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EXAMPLE 21

L-Cysteinyl-4-acetamido-4-(2-methylbenzyl)piperidine trifluoroacetic acid salt

Step 1: Preparation of N-t-butoxycarbonyl-4-amino-4-(2-methylbenzyl)piperidine

To a mixture of 4-(2-methylbenzyl) N-t-butoxycarbonyl isonipecotic acid (1.0 g, 3.0 mmol) in CH₃CN (20 ml) add diphenyl phosphoryl azide (0.99 g, 3.6 mmol) and triethylamine (0.50 ml, 3.6 mmol). After stirring at 55°C (oil bath temp.) concentrate the reaction in vacuo and partition the residue between EtOAc and saturated aqueous NaHCO₃. The organic phase is washed with brine, dried (MgSO₄), and concentrated in vacuo to afford the crude product.

Step 2: Preparation of N-t-butoxycarbonyl-4-acetamido-4-(2-methylbenzyl)piperidine

A mixture of N-t-butoxycarbonyl-4-amino-4-(2-methylbenzyl)piperidine (305 mg, 1.0 mmol), acetic anhydride (0.38 ml, 4.0 mmol), and pyridine (0.1 ml, 1.2 mmol) in CH₂Cl₂ is stirred at room temp. overnight. Then concentrate the reaction mixture in vacuo and purify the residue by column chromatography on silica to afford the product.

Step 3: Preparation of 4-Acetamido-4-(2-methylbenzyl)piperidine hydrochloride salt

The N-t-butoxycarbonyl deprotection procedure as described above in Example 1, Step 6 is utilized to afford the product.

Step 4: Preparation of N-t-butoxycarbonyl-S-trityl-L-Cysteinyl-4-acetamido-4-(2-methylbenzyl)piperidine

The coupling procedure as described above in Example 1, Step 7 is utilized to afford the product.

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Step 5: Preparation of L-Cysteinyl-4-acetamido-4-(2-methylbenzyl)piperidine trifluoroacetic acid salt

Cysteine deprotection as described above in Example 1,
Step 8 affords the product.

EXAMPLE 22

L-Cysteinyl-4-methylsulfonamido-4-(2-methylbenzyl)piperidine
trifluoroacetic acid salt

Step 1: Preparation of N-t-butoxycarbonyl-4-methylsulfonamido-4-(2-methylbenzyl)piperidine

A mixture of N-t-butoxycarbonyl-4-amino-4-(2-methylbenzyl)piperidine (305 mg, 1.0 mmol), methane-sulfonyl chloride (0.31 ml, 4.0 mmol), and pyridine (0.1 ml, 1.2 mmol) in CH₂Cl₂ (2 mL) is stirred at room temp. overnight. Then concentrate the reaction mixture in vacuo and purify the residue by column chromatography on silica to afford the product.

Step 2: Preparation of 4-Methylsulfonamido-4-(2-methylbenzyl)piperidine hydrochloride salt

The N-t-butoxycarbonyl deprotection procedure as described above in Example 1, Step 6 is utilized to afford the product.

Step 3: Preparation of N-t-butoxycarbonyl-S-trityl-L-Cysteinyl-4-methylsulfonamido-4-(2-methylbenzyl)piperidine

The coupling procedure as described above in Example 1, Step 7 is utilized to afford the product.

Step 4: Preparation of L-Cysteinyl-4-methylsulfonamido-4-(2-methylbenzyl)piperidine trifluoroacetic acid salt

Cysteine deprotection as described above in Example 1, Step 8 affords the product.

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EXAMPLE 23In vitro inhibition of ras farnesyl transferase

5 Farnesyl-protein transferase (FTase) from bovine brain was chromatographed on DEAE-Sephacel (Pharmacia, 0-0.8 M NaCl gradient elution), N-octyl agarose (Sigma, 0-0.6 M NaCl gradient elution), and a mono Q HPLC column (Pharmacia, 0-0.3 M NaCl gradient). Ras-CVLS at 3.5 μ M, 0.25 μ M [3 H]FPP, and the indicated
10 compounds were incubated with either a partially purified bovine enzyme preparation or a recombinant human enzyme preparation. The recombinant human enzyme was prepared as described in Omer, C.A., Kral, A.M., Diehl, R.E., Prendergast, G.C., Powers, S., Allen, C.M., Gibbs, J.B. and Kohl, N.E. (1993) Biochemistry 32:5167-5176. The
15 FTase data presented reflects the ability of the test compound to inhibit RAS farnesylation in vitro, as described in Pompliano, et al., Biochemistry 31:3800 (1992).

20 In the above assay, the compounds, as listed on pages 6-8, demonstrated the ability to inhibit RAS farnesylation at a concentration of 10 μ M or less. For the preferred compounds, listed on pages 8 to 9, activity was exhibited at 2 μ M or less.

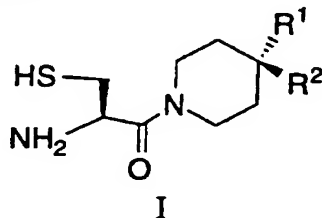
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WHAT IS CLAIMED IS:

1. A compound which inhibits farnesyl-protein transferase of the Formula I:



wherein:

R¹ is selected from:

- a) COR,
- b) CO₂R,
- c) CONHR,
- d) OH,
- e) OCOR,
- f) CN,
- g) CH₂OR,
- h) NHCOR,
- i) NHSO₂R, or
- j) COR⁵;

R is selected from:

- a) C₁₋₄ alkyl, unsubstituted or substituted with:
 - i) C₁₋₄ alkoxy,
 - ii) NR³R⁴,
 - iii) C₃₋₆ cycloalkyl,
 - iv) aryl or heterocycle; or
- b) aryl or heterocycle;

R² is selected from: aryl, aralkyl, heterocycle, or heteroaralkyl, unsubstituted or substituted with one or more of:

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- 5
- a) C₁₋₄ alkyl, unsubstituted or substituted with:
- i) C₁₋₄ alkoxy,
 - ii) NR³R⁴,
 - iii) C₃₋₆ cycloalkyl, or
 - iv) aryl or heterocycle;
- b) aryl or heterocycle,
- c) halogen,
- d) OR³,
- 10 e) NR³R⁴,
- f) CN,
- g) NO₂, or
- h) CF₃;
- 15 R³ and R⁴ are independently selected from: H, C₁₋₄ alkyl, C₃₋₆ cycloalkyl, heterocycle, aryl, aroyl, heteroaryl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with one or more of:
- a) C₁₋₄ alkoxy,
 - b) aryl or heterocycle,
 - c) halogen, or
 - 20 d) HO, wherein

or R³ and R⁴ may be joined in a ring;

- 25 R⁵ is selected from:
- a) a naturally occurring amino acid, or
 - b) an oxidized form of a naturally occurring amino acid which is:
 - i) methionine sulfoxide, or
 - 30 ii) methionine sulfone;

or the pharmaceutically acceptable salt thereof.

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2. A compound according to Claim 1 which is selected from the group consisting of:

5 L-Cysteinyl-4-(2-methylbenzyl)isonipecotyl-L-methionine;

L-Cysteinyl-4-benzyl isonipecotic acid methyl ester;

L-Cysteinyl-4-(2-methylbenzyl)isonipecotyl N-methyl amide;

10 L-Cysteinyl-4-(2-methylbenzyl)isonipecotyl N-(2-pyridylmethyl)
amide;

L-Cysteinyl-4-(2-methylbenzyl)isonipecotyl N-benzyl amide;

15 L-Cysteinyl-4-(2-methylbenzyl)isonipecotic acid methyl ester;

L-Cysteinyl-4-(2-chlorobenzyl)isonipecotic acid methyl ester;

20 L-Cysteinyl-4-(2,3-dichlorobenzyl)isonipecotic acid methyl ester;

L-Cysteinyl-4-(2,4-dichlorobenzyl)isonipecotic acid methyl ester;

L-Cysteinyl-4-(2,6-dichlorobenzyl)isonipecotic acid methyl ester;

25 L-Cysteinyl-4-(3-(2-methyl)pyridylmethyl)isonipecotic acid methyl
ester;

L-Cysteinyl-4-(1-naphthyl)methyl isonipecotic acid methyl ester;

30 L-Cysteinyl-4-(1-naphthyl)methyl isonipecotic acid ethyl ester;

L-Cysteinyl-4-(1-naphthyl)methyl isonipecotic acid benzyl ester;

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L-Cysteinyl-4-(2-methylbenzyl)isonipecotic acid 2-pyridylmethyl ester;

5 L-Cysteinyl-4-(2-methylbenzyl)isonipecotic acid 3-pyridylmethyl ester;

L-Cysteinyl-4-(2-methylbenzyl)isonipecotic acid 4-pyridylmethyl ester;

10 L-Cysteinyl-4-benzyl-4-piperidinol;

L-Cysteinyl-4-acetoxy-4-benzylpiperidine;

15 L-Cysteinyl-4-cyano-4-phenylpiperidine;

L-Cysteinyl-4-acetyl-4-phenylpiperidine;

L-Cysteinyl-4-methoxymethyl-4-(2-methylbenzyl)piperidine;

20 L-Cysteinyl-4-acetamido-4-(2-methylbenzyl)piperidine;

L-Cysteinyl-4-methylsulfonamido-4-(2-methylbenzyl)piperidine;

25 or the pharmaceutically acceptable salts.

3. A compound according to Claim 2 that inhibits farnesyl-protein transferase which is:

30 L-Cysteinyl-4-(2-methylbenzyl)isonipecotyl N-methyl amide;

L-Cysteinyl-4-(2-methylbenzyl)isonipecotyl N-(2-pyridylmethyl) amide;

L-Cysteinyl-4-(2-methylbenzyl)isonipecotyl N-benzyl amide;

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L-Cysteiny-4-(2-methylbenzyl)isonipecotic acid methyl ester;

5 L-Cysteiny-4-(2-chlorobenzyl)isonipecotic acid methyl ester;

L-Cysteiny-4-(2,3-dichlorobenzyl)isonipecotic acid methyl ester;

L-Cysteiny-4-(2,4-dichlorobenzyl)isonipecotic acid methyl ester;

10 L-Cysteiny-4-(2,6-dichlorobenzyl)isonipecotic acid methyl ester;

L-Cysteiny-4-(3-(2-methyl)pyridylmethyl)isonipecotic acid methyl ester;

15 L-Cysteiny-4-(1-naphthyl)methyl isonipecotic acid methyl ester;

L-Cysteiny-4-(1-naphthyl)methyl isonipecotic acid ethyl ester;

20 L-Cysteiny-4-(1-naphthyl)methyl isonipecotic acid benzyl ester;

L-Cysteiny-4-(2-methylbenzyl) isonipecotic acid 2-pyridylmethyl ester;

25 L-Cysteiny-4-(2-methylbenzyl) isonipecotic acid 3-pyridylmethyl ester;

L-Cysteiny-4-(2-methylbenzyl) isonipecotic acid 4-pyridylmethyl ester;

30 L-Cysteiny-4-benzyl-4-piperidinol;

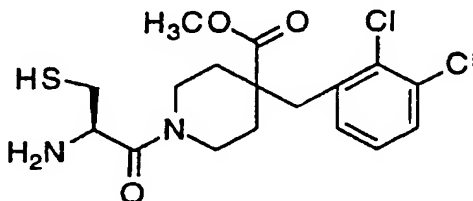
L-Cysteiny-4-methoxymethyl-4-(2-methylbenzyl)piperidine;

or the pharmaceutically acceptable salts thereof.

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4. The compound which is:

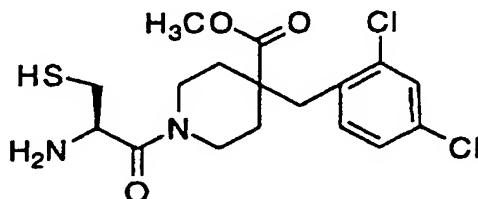
5 L-Cysteinyl-4-(2,3-dichlorobenzyl)isonipecotic acid methyl ester



or a pharmaceutically acceptable salt thereof.

5. The compound which is:

15 L-Cysteinyl-4-(2,4-dichlorobenzyl)isonipecotic acid methyl ester



or a pharmaceutically acceptable salt thereof.

25 6. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 1.

30 7. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 2.

8. A method for inhibiting farnesyl-protein transferase which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 6.

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5 9. A method for inhibiting farnesyl-protein transferase
which comprises administering to a mammal in need thereof a
therapeutically effective amount of a composition of Claim 7.

10 10. A method for treating cancer which comprises
administering to a mammal in need thereof a therapeutically effective
amount of a composition of Claim 6.

15 11. A method for treating cancer which comprises
administering to a mammal in need thereof a therapeutically effective
amount of a composition of Claim 7.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/10827

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : Please See Extra Sheet.

US CL : Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 94/26723 (MARSTERS ET AL) 24 NOVEMBER 1994, PAGE 169, LINES 4 + .	1-11
A	US, A, 5,326,773 (DE SOLMS ET AL) 05 JULY 1994.	1-11
A	US, A, 5,238,922 (GRAHAM ET AL) 24 AUGUST 1993	1-11
A	US, A, 5,043,268 (STOCK) 27 AUGUST 1991.	1-11

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X*	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y*	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Z*	document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means		
P document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

17 NOVEMBER 1995

Date of mailing of the international search report

02 JAN 1996

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Form PCT/ISA/210 (second sheet)(July 1992)*

A. CLASSIFICATION OF SUBJECT MATTER:

IPC (6):

A61K 31/435, 31/44, 31/445, 31/495, 31/54, 31/545; C07D 211/06, 211/22, 211/32, 211/40, 211/54, 211/56, 401/06, 401/10, 401/12, 405/02, 405/14, 409/02, 409/10, 409/12, 409/14, 413/02, 413/10, 413/12, 413/14, 417/02, 417/10, 417/12, 417/14

A. CLASSIFICATION OF SUBJECT MATTER:

US CL :

514/315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 329, 330; 546/187, 188, 189, 193, 194, 195, 196, 197, 198, 199, 200, 201, 207, 208, 209, 210, 212, 213, 214, 215, 216, 217, 218, 221, 223, 224, 226

B. FIELDS SEARCHED

Minimum documentation searched

Classification System: U.S.

514/315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 329, 330; 546/187, 188, 189, 193, 194, 195, 196, 197, 198, 199, 200, 201, 207, 208, 209, 210, 212, 213, 214, 215, 216, 217, 218, 221, 223, 224, 226